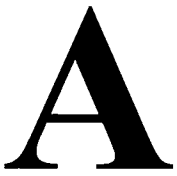
DO NOT ENTER: /C.S./



DO NOT ENTER: /C.S./

11-14-05

1636


Please type a plus sign (+) inside this box [+]

PTO/SB/21 (6-99)
Approved for use through 09/30/2000. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

| | |
|---|---|
| Application Number | 09/903,640 |
| Filing Date | JULY 11, 2001 |
| First Named Inventor | AVI ASHKENAZI |
| Group/Art Unit | 1636 |
| Examiner Name | KATCHEVES, KONSTANTINA T. |
| Total Number of Pages in This Submission: 20 | Attorney Docket Number: 39780-1618 P2C48 |

**ENCLOSURES** *(check all that apply)*

- [ ] Fee Transmittal Form
  - [ ] Fee Attached
- [x] **AMENDMENT / RESPONSE**
  - [ ] After Final
  - [ ] Version With Markings Showing Changes
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
  - [ ] Copy of Notice
- [ ] Copy of an Assignment
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition Routing Slip (PTO/SB/69) and Accompanying Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, by Assignee to Exclusion of Inventor Under 37 C.F.R. §3.71 With Revocation of Prior Powers
- [ ] Terminal Disclaimer
- [ ] Small Entity Statement
- [ ] Request for Refund
- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [x] **ADDITIONAL ENCLOSURE(S)** ***(PLEASE IDENTIFY BELOW):***
  - [x] **COPY OF ARTICLE BY BEER, ET AL.; and STAMPED RETURN POSTCARD**

Remarks

**AUTHORIZATION TO CHARGE DEPOSIT ACCOUNT 08-1641 FOR ANY FEES DUE IN CONNECTION WITH THIS PAPER, REFERENCING ATTORNEY'S DOCKET NO. 39780-1618 P2C48.**

**SIGNATURE OF APPLICANT, ATTORNEY OR AGENT**

| | | | |
|---|---|---|---|
| Firm or Individual name | HELLER EHRMAN LLP | PANPAN GAO (Reg. No. 43,626) | |
| | 275 Middlefield Road, Menlo Park, California 94025 | Telephone: (650) 324-7000 | Facsimile: (650) 324-0638 |
| Signature | | | |
| Date | NOVEMBER 9, 2005 | Customer Number: | 35489 |

**CERTIFICATE OF EXPRESS MAILING**

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated below and addressed to: **MAIL STOP AMENDMENT,** Commissioner for Patents, PO Box 1450, Alexandria, Virginia 22313-1450, on this date: **NOVEMBER 9, 2005**

Express Mail Label **EV 765 989 469 US**

| | | | |
|---|---|---|---|
| Typed or printed name | C. FONG | | |
| Signature | C. F | Date | NOVEMBER 9, 2005 |

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop ___, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| In re application of: | ) | Examiner: Katcheves, Konstantina T. |
| Avi ASHKENAZI, et al. | ) | Art Unit: 1636 |
| Application Serial No. 09/903,640 | ) | Confirmation No. 3104 |
| Filed: July 11, 2001 | ) | Attorney's Docket No. 39780-1618 P2C48 |
| For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME** | ) | **Customer No. 35489** |

**EXPRESS MAIL LABEL NO. EV 765 989 469 US**
**DATE MAILED: NOVEMBER 9, 2005**

## AMENDMENT AND RESPONSE TO OFFICE ACTION

**MAIL STOP AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action mailed on August 9, 2005 in connection with the above-identified patent application (Paper No./Mail Date 0522), please enter the following amendments, and consider the following arguments. This response is timely filed within the shortened statutory period set for the response hence no fees are believed due. Enclosed is a copy of article by Beer *et al.*, Nature Medicine 8(8) 816-824 (2002) for the Examiner's reference, consideration of which is respectfully requested.

**Amendments to the Claims** are reflected in the listing of claims that begins on page 2 of this paper.

**Remarks/Arguments** begin on page 4 of this paper.

**Amendments to the Claims:**

1-43. (canceled)

44. (previously presented) An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 263;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481;

wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors.

45. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263.

46. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 263, lacking its associated signal peptide.

47. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 263.

48. (canceled)

49. (previously presented) The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209481.

50. (previously presented) A chimeric polypeptide comprising a polypeptide according to Claim 44 fused to a heterologous polypeptide.

51. (previously presented) The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

## REMARKS/ARGUMENTS

Claims 44-47 and 49-51 are pending in this application. The rejections to the claims are respectfully traversed.

### Claim Rejections-35 U.S.C. §§101/112, First Paragraph

Claims 44-47 and 49-51 are rejected under 35 U.S.C. §101, allegedly because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

Claims 44-47 and 49-51 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejection. With respect to Claims 44-47 and 49-51, Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the PRO343 polypeptides possess a credible, specific and substantial asserted utility and are fully enabled.

Applicants have asserted utility for the instantly claimed PRO343 polypeptide based on amplification of the PRO343 gene in the "gene amplification assay" described in the instant specification in Example 92. Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 92 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 230-234 of the specification), including primary lung and colon cancers of the type and stage indicated in Table 8 (page 227). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 222, lines 34-36). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. As explained in the passage bridging pages 222 and 223, the results of TaqMan™ PCR are reported in ΔCt units. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification. PRO343 showed

ΔCt values of approximately 1.00-3.62 in seven lung tumors and 1.15-3.49 thirteen colon tumors. This corresponds to at least **2.00- 12.3 fold amplification in lung tumors** and at least **2.22- 11.24 fold amplification in colon tumors**. Accordingly, the present specification clearly discloses strong evidence that the gene encoding the PRO343 polypeptide is significantly amplified in a significant number of lung and colon tumors.

In further support for the "significance" of the amplification, Applicants had submitted, in their Response filed March 11, 2003, a Declaration by Dr. Audrey Goddard. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

In addition, the Goddard Declaration clearly establishes that the TaqMan real-time PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO343 is a diagnostic marker of lung or colon cancer.

The Examiner notes that "the present claims are drawn to the polypeptide PRO343, not the polynucleotide" and therefore, there is allegedly, no specific, credible or substantial utility for the claimed polypeptides. The Examiner quotes Chen *et al.* to support this view.

Applicants submit that they had presented supportive evidence with their response mailed August 11, 2004 to show that the art generally teaches that "it is more likely than not" for amplified genes to also result in increased mRNA and protein levels. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, collectively teach that in general, gene

amplification increases mRNA expression. For instance, Ornfoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Ornfoft *et al.* showed a clear correlation between mRNA and protein expression levels in the proteins they studied and state that, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornfoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

Similarly Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Second, the Declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels.

Applicants further submit that, contrary to the Examiner's assertion, the cited Chen *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO343 polypeptide. For instance, Applicants note that the proteins selected for their study in Chen *et al.* were identified by staining of 2D gels. As is well known, there are problems with selecting proteins detectable by 2D gels: "It is apparent that without prior enrichment only a relatively small and highly selected population of *long-lived, highly expressed proteins* is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is

the low abundance proteins that execute key regulatory functions" (page 1870, col. 1). Thus, Chen *et al.*, by selecting proteins visualized by 2D gels, are likely to have excluded in their analysis many key regulatory proteins which could be candidate cancer markers.

Secondly, the manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. The authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. This resulted in negative normalized protein values in some cases and the authors concluded that it is not possible *to predict* overall protein expression based on **average mRNA abundance**. Once again, Applicants remind the Examiner that the utility standard does not require accurate prediction of protein values; only that in a majority of the proteins studied, it is more likely than not that protein levels increased when mRNA levels increased. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not". Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. No genes showed a significant negative correlation. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

The same authors in Chen *et al.*, published a later paper, Beer *et al.*, Nature Medicine 8(8) 816-824 (2002) (copy enclosed) which described gene expression of genes in adenocarcinomas

and compared that to protein expression. In this paper they report that "these results suggest that the oligonucleotide microarrays provided reliable measures of gene expression." (pg 317). The authors also state "these studies indicate that many of the genes identified using gene expression profiles are likely relevant to lung adenocarcinoma." Clearly the authors of the Chen paper agree that microarrays provide a reliable measure of the expression levels of the gene and can be used to identify genes whose overexpression is associated with tumors.

As was discussed in the Utility standard submitted in previous responses, the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. Accordingly, the data by Chen *et al.* confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's Utility rejection is based on a misrepresentation of the scientific data presented in Chen *et al.* and by applying an improper, heightened legal standard in this case. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the mRNA and the encoded protein will also be expressed at an elevated level. As noted even in Chen *et al.* most genes showed a correlation between increased mRNA and translated protein.

The Examiner also notes that "the claimed sequences merely revealed similarity to proteases in genenral" (page 3, last paragraph of Office action). Applicants respectfully assert that utility for the instant PRO343 is based on the results in the gene amplification assay, not on structure prediction, and hence such a rejection is moot.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the Polakis Declaration and the widespread use of array chips, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO343 gene, that the PRO343 polypeptide is concomitantly overexpressed.

Thus, Applicants have demonstrated utility for the PRO343 polypeptide based on the gene amplification assay and thus, Applicants request that the Examiner reconsider the utility for the present application based on the present arguments. Furthermore, since the specification has provided detailed protocols for the gene amplification assay, for example, in Example 92, one of ordinary skill in the art could identify that the claimed polypeptides could be made and used in the diagnosis of lung or colon tumors, without any undue experimentation.

Hence Applicants respectfully request reconsideration and reversal of the utility/ enablement rejection of the pending claims under 35 U.S.C. §§101/112, first paragraph.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C48**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 9, 2005

By:_____
Panpan Gao (Reg. No. 43,626)

**HELLER EHRMAN, LLP**
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2166627 v1
11/9/05 11:15 AM (39780.1618)